FUZEON™ (enfuvirtide)

27898287

Prescribing Information

Roche

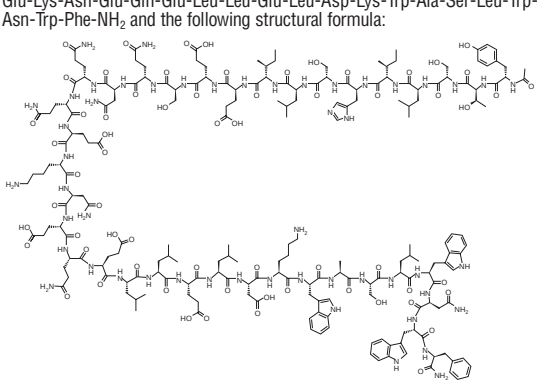
FUZEON™ (enfuvirtide) for Injection

DESCRIPTION

FUZEON (enfuvirtide) is an inhibitor of the fusion of HIV-1 with CD4+ cells. Enfuvirtide is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carboxamide. It is composed of naturally occurring L-amino acid residues.

Enfuvirtide is a white to off-white amorphous solid. It has negligible solubility in pure water and the solubility increases in aqueous buffers (pH 7.5) to 85-142 g/100 mL. The empirical formula of enfuvirtide is $C_{204}H_{301}N_{51}O_{64}$, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH_3CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_2 and the following structural formula:



The drug product, FUZEON (enfuvirtide) for Injection, is a white to off-white, sterile, lyophilized powder. Each single-use vial contains 108 mg of enfuvirtide for the delivery of 90 mg. Prior to subcutaneous administration, the contents of the vial are reconstituted with 1.1 mL of Sterile Water for Injection giving a volume of approximately 1.2 mL to provide the delivery of 1 mL of the solution. Each 1 mL of the reconstituted solution contains approximately 90 mg of enfuvirtide with approximate amounts of the following excipients: 22.55 mg of mannitol, 2.39 mg of sodium carbonate (anhydrous), and sodium hydroxide and hydrochloric acid for pH adjustment as needed. The reconstituted solution has an approximate pH of 9.0.

MICROBIOLOGY

Mechanism of Action

Enfuvirtide interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes.

Antiviral Activity In Vitro

The in vitro antiviral activity of enfuvirtide was assessed by infecting different CD4+ cell types with laboratory and clinical isolates of HIV-1. The IC_{50} (50% inhibitory concentration) for enfuvirtide in laboratory and primary isolates representing HIV-1 clades A to G ranged from 4 to 280 nM (18 to 1260 ng/mL). The IC_{50} for baseline clinical isolates ranged from 0.089 to 107 nM (0.4 to 480 ng/mL) by the cMAGI assay (n=130) and from 1.56 to 1680 nM (7 to 7530 ng/mL) by a recombinant phenotypic entry assay (n=612). Enfuvirtide was similarly active in vitro against R5, X4, and dual tropic viruses. Enfuvirtide has no activity against HIV-2.

Enfuvirtide exhibited additive to synergistic effects in cell culture assays when combined with individual members of various antiretroviral classes, including zidovudine, lamivudine, nelfinavir, indinavir, and efavirenz.

Drug Resistance

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro. Genotypic analysis of the in vitro-selected resistant isolates showed mutations that resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36 to 38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed mutants in positions 36 to 38 in an HIV-1 molecular clone showed a 5-fold to 684-fold decrease in susceptibility to enfuvirtide.

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects treated with FUZEON in combination with other antiretroviral agents. Posttreatment HIV-1 virus from 185 subjects exhibited decreases in susceptibility to enfuvirtide ranging from 4-fold to 422-fold relative to their respective baseline virus and exhibited genotypic changes in gp41 amino acids 36 to 45. Substitutions in this region were observed with decreasing frequency at amino acid positions 38, 43, 36, 40, 42, and 45.

Cross-resistance

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were susceptible to enfuvirtide in cell culture.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic properties of enfuvirtide were evaluated in HIV-1 infected adult and pediatric patients.

Absorption

Following a 90-mg single subcutaneous injection of FUZEON into the abdomen in 12 HIV-1 infected subjects, the mean (±SD) C_{max} was 4.59 ± 1.5 µg/mL, AUC was 55.8 ± 12.1 µg·h/mL and the median T_{max} was 8 hours (ranged from 3 to 12 h). The absolute bioavailability (using a 90-mg intravenous dose as a reference) was 84.3% ± 15.5%. Following 90-mg bid dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean (±SD) steady-state C_{max} was 5.0 ± 1.7 µg/mL, C_{trough} was 3.3 ± 1.6 µg/mL, $AUC_{0\text{-}12h}$ was 48.7 ± 19.1 µg·h/mL, and the median T_{max} was 4 hours (ranged from 4 to 8 h).

Absorption of the 90-mg dose was comparable when injected into the subcutaneous tissue of the abdomen, thigh or arm.

Distribution

The mean (±SD) steady-state volume of distribution after intravenous administration of a 90-mg dose of FUZEON (N=12) was 5.5 ± 1.1 L.

Enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma over a concentration range of 2 to 10 µg/mL. It is bound predominantly to albumin and to a lower extent to α-1 acid glycoprotein.

Metabolism/Elimination

As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.

Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans.

In vitro studies with human microsomes and hepatocytes indicate that enfuvirtide undergoes hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine residue, M3. The hydrolysis reaction is not NADPH dependent. The M3 metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4% to 15% of the enfuvirtide AUC.

Following a 90-mg single subcutaneous dose of enfuvirtide (N=12) the mean ±SD elimination half-life of enfuvirtide is 3.8 ± 0.6 h and the mean ±SD apparent clearance was 24.8 ± 4.1 mL/h/kg. Following 90-mg bid dosing of FUZEON subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean ±SD apparent clearance was 30.6 ± 10.6 mL/h/kg.

Special Populations

Hepatic Insufficiency

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with hepatic impairment.

Renal Insufficiency

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with renal insufficiency. However, analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is not affected in patients with creatinine clearance greater than 35 mL/min. The effect of creatinine clearance less than 35 mL/min on enfuvirtide clearance is unknown.

Gender and Weight

GENDER

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is 20% lower in females than males after adjusting for body weight.

WEIGHT

Enfuvirtide clearance decreases with decreased body weight irrespective of gender. Relative to the clearance of a 70-kg male, a 40-kg male will have 20% lower clearance and a 110-kg male will have a 26% higher clearance. Relative to a 70-kg male, a 40-kg female will have a 36% lower clearance and a 110-kg female will have the same clearance.

No dose adjustment is recommended for weight or gender.

Race

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide was not different in Blacks compared to Caucasians. Other pharmacokinetic studies suggest no difference between Asians and Caucasians after adjusting for body weight.

Pediatric Patients

The pharmacokinetics of enfuvirtide have been studied in 18 pediatric subjects aged 6 through 16 years at a dose of 2 mg/kg. Enfuvirtide pharmacokinetics were determined in the presence of concomitant medications including antiretroviral agents. A dose of 2 mg/kg bid (maximum 90 mg bid) provided enfuvirtide plasma concentrations similar to those obtained in adult patients receiving 90 mg bid.

In the 18 pediatric subjects receiving the 2 mg/kg bid dose, the mean ±SD steady-state AUC was 53.6 ± 21.4 µg·h/mL, C_{max} was 5.9 ± 2.2 µg/mL, C_{trough} was 3.0 ± 1.5 µg/mL, and apparent clearance was 40 ± 14 mL/h/kg.

Geriatric Patients

The pharmacokinetics of enfuvirtide have not been studied in patients over 65 years of age.

Drug Interactions

Influence of FUZEON on the Metabolism of Concomitant Drugs

Based on the results from an in vitro human microsomal study, enfuvirtide is not an inhibitor of CYP450 enzymes. In an in vivo human metabolism study (N=12), FUZEON at the recommended dose of 90 mg bid did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19 or CYP2E1 substrates.

Influence of Concomitant Drugs on the Metabolism of Enfuvirtide

In separate pharmacokinetic interaction studies, coadministration of ritonavir (N=12), saquinavir/ritonavir (N=12), and rifampin (N=12) did not result in clinically significant pharmacokinetic interactions with FUZEON (see Table 1).

Table 1. Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on the Steady-State Pharmacokinetics of Enfuvirtide (90 mg bid)*

Coadministered Drug	Dose of Coadministered Drug	N	% Change of Enfuvirtide Pharmacokinetic Parameters† (90% CI)		
			C_{max}	AUC	C_{trough}
Ritonavir	200 mg, q12h, 4 days	12	↑24 (↑9 to ↑41)	↑22 (↑8 to ↑37)	↑14 (↑2 to ↑28)
Saquinavir/ Ritonavir	1000/100 mg, q12h, 4 days	12	⇔	↑14 (↑5 to ↑24)	↑26 (↑17 to ↑35)
Rifampin	600 mg, qd, 10 days	12	⇔	⇔	↓15 (↓22 to ↓7)

*All studies were performed in HIV-1+ subjects using a sequential crossover design.
†↑ = Increase; ↓ = Decrease; ⇔ = No Effect (↑ or ↓ <10%)

INDICATIONS AND USAGE

FUZEON in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of FUZEON of 24 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of FUZEON in antiretroviral naive patients. There are no results from controlled trials evaluating the effect of FUZEON on clinical progression of HIV-1.

Description of Clinical Studies

Studies in Antiretroviral Experienced Patients

Studies T20-301 and T20-302 are ongoing, randomized, controlled, open-label, multicenter trials in HIV-1 infected subjects. Subjects were required to have either (1) viremia despite 3 to 6 months prior therapy with a nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI) or (2) viremia and documented resistance or intolerance to at least one member in each of the NRTI, NNRTI, and PI classes.

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All subjects received an individualized background regimen consisting of 3 to 5 antiretroviral agents selected on the basis of the subject's prior treatment history and baseline genotypic and phenotypic viral resistance measurements. Subjects were then randomized at a 2:1 ratio to FUZEON 90 mg bid with background regimen or background regimen alone.

Demographic characteristics for studies T20-301 and T20-302 are shown in Table 2. Subjects had prior exposure to a median of 12 antiretrovirals for a median of 7 years.

Table 2. T20-301 and T20-302 Pooled Subject Demographics

	FUZEON+ Background Regimen	Background Regimen
	N=661	N=334
Sex Male Female	 90% 10%	 90% 10%
Race White Black	 89% 8%	 89% 7%
Mean Age (yr) (range)	43 (16-67)	43 (24-82)
Median Baseline HIV-1 RNA (log_{10} copies/mL)	5.2 (3.5-6.7)	5.1 (3.7-7.1)
Median Baseline CD4 Cell Count (cells/mm^3)	88 (1-994)	97 (1-847)

The change in plasma HIV-1 RNA from baseline to week 24 was -1.52 log_{10} copies/mL for subjects receiving FUZEON plus background regimen compared to -0.73 log_{10} copies/mL for subjects receiving the background regimen only (see Table 3).

Subjects with two or more active drugs in their background regimen were more likely to achieve a HIV-1 RNA of <400 copies/mL.

Table 3. Outcomes of Randomized Treatment at Week 24 (Pooled Studies T20-301 and T20-302)

Outcomes	FUZEON+ Background Regimen 90 mg bid	Background Regimen
	N=661	N=334
HIV-1 RNA Log Change from Baseline (log_{10} copies/mL)*	-1.52	-0.73
CD4+ cell count Change from Baseline (cells/mm^3)#	+71	+35
HIV RNA ≥1 log below Baseline	342 (52%)	86 (26%)
HIV RNA <400 copies/mL	247 (37%)	54 (16%)
HIV RNA <50 copies/mL	151 (23%)	30 (9%)
Discontinued due to adverse reactions/labs†	40 (6%)	12 (4%)
Discontinued due to injection site reactions†	20 (3%)	N/A
Discontinued due to other reasons†ϕ§	36 (5%)	14 (4%)

* Based on results from pooled data of T20-301 and T20-302 on ITT population (week 24 viral load for subjects who were lost to follow-up, discontinued therapy, or switched from their original randomization, is replaced by their baseline value).
# Last value carried forward.
† Percentages based on safety population FUZEON+background (N=663) and background (N=337).
ϕ As per the judgment of the investigator.
§ Includes discontinuations from loss to follow-up, treatment refusal, and other reasons.

CONTRAINDICATIONS

FUZEON is contraindicated in patients with known hypersensitivity to FUZEON or any of its components (see WARNINGS).

WARNINGS

Local Injection Site Reactions

The most common adverse events associated with FUZEON use are local injection site reactions. Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Nine percent of patients had local reactions that required analgesics or limited usual activities (see ADVERSE REACTIONS). Reactions are often present at more than one injection site. Patients must be familiar with the FUZEON *Injection Instructions* in order to know how to inject FUZEON appropriately and how to monitor carefully for signs or symptoms of cellulitis or local infection.

Pneumonia

An increased rate of bacterial pneumonia was observed in subjects treated with FUZEON in the Phase 3 clinical trials compared to the control arm (see ADVERSE REACTIONS). It is unclear if the increased incidence of pneumonia is related to FUZEON use. However, because of this finding, patients with HIV infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia. Risk factors for pneumonia included low initial CD4 cell count, high initial viral load, intravenous drug use, smoking, and a prior history of lung disease (see ADVERSE REACTIONS).

Hypersensitivity Reactions

Hypersensitivity reactions have been associated with FUZEON therapy and may recur on re-challenge. Hypersensitivity reactions have included individually and in combination: rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum liver transaminases. Other adverse events that may be immune mediated and have been reported in subjects receiving FUZEON include primary immune complex reaction, respiratory distress glomerulonephritis, and Guillain-Barre syndrome. Patients developing signs and symptoms suggestive of a systemic hypersensitivity reaction should discontinue FUZEON and should seek medical evaluation immediately. Therapy with FUZEON should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction. Risk factors that may predict the occurrence or severity of hypersensitivity to FUZEON have not been identified (see ADVERSE REACTIONS).

PRECAUTIONS

Non-HIV Infected Individuals

There is a theoretical risk that FUZEON use may lead to the production of anti-enfuvirtide antibodies which cross react with HIV gp41. This could result in a false positive HIV test with an ELISA assay; a confirmatory western blot test would be expected to be negative. FUZEON has not been studied in non-HIV infected individuals.

Information for Patients

To assure safe and effective use of FUZEON, the following information and instructions should be given to patients:

- Patients should be informed that injection site reactions occur commonly. Patients must be familiar with the FUZEON *Injection Instructions* for instructions on how to appropriately inject FUZEON and how to carefully monitor for signs or symptoms of cellulitis or local infection. Patients should be instructed when to contact their healthcare provider about these reactions.
- Patients should be made aware that an increased rate of bacterial pneumonia was observed in subjects treated with FUZEON in Phase 3 clinical trials compared to the control arm. Patients should be advised to seek medical evaluation immediately if they develop signs or symptoms suggestive of pneumonia (cough with fever, rapid breathing, shortness of breath) (see WARNINGS).
- Patients should be advised of the possibility of a hypersensitivity reaction to FUZEON. Patients should be advised to discontinue therapy and immediately seek medical evaluation if they develop signs/symptoms of hypersensitivity (see WARNINGS).
- FUZEON is not a cure for HIV-1 infection and patients may continue to contract illnesses associated with HIV-1 infection. The long-term effects of FUZEON are unknown at this time. FUZEON therapy has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.
- FUZEON must be taken as part of a combination antiretroviral regimen. Use of FUZEON alone may lead to rapid development of virus resistant to FUZEON and possibly other agents of the same class.
- Patients and caregivers must be instructed in the use of aseptic technique when administering FUZEON in order to avoid injection site infections. Appropriate training for FUZEON reconstitution and self-injection must be given by a healthcare provider, including a careful review of the FUZEON Patient Package Insert and FUZEON *Injection Instructions*. The first injection should be performed under the supervision of an appropriately qualified healthcare provider. It is recommended that the patient and/or caregiver's understanding and use of aseptic self-injection techniques and procedures be periodically re-evaluated.
- Patients should contact their healthcare provider for any questions regarding the administration of FUZEON. Patients should be told not to reuse needles or syringes, and be instructed in safe disposal procedures including the use of a puncture-resistant container for disposal of used needles and syringes. Patients must be instructed on the safe disposal of full containers as per local requirements. Caregivers who experience an accidental needlestick after patient injection should contact a healthcare provider immediately.
- Patients should inform their healthcare provider if they are pregnant, plan to become pregnant or become pregnant while taking this medication.
- Patients should inform their healthcare provider if they are breast-feeding.
- Patients should not change the dose or dosing schedule of FUZEON or any antiretroviral medication without consulting their healthcare provider.
- Patients should contact their healthcare provider immediately if they stop taking FUZEON or any other drug in their antiretroviral regimen.
- Patients should be told that they can obtain more information on the self-administration of FUZEON at www.FUZEON.com or by calling 1-877-4-FUZEON (1-877-438-9366).

Patients should be advised that no studies have been conducted on the ability to drive or operate machinery while taking FUZEON. If patients experience dizziness while taking FUZEON, they should be advised to talk to their healthcare provider before driving or operating machinery.

Drug Interactions

CYP450 Metabolized Drugs

Results from in vitro and in vivo studies suggest that enfuvirtide is unlikely to have significant drug interactions with concomitantly administered drugs metabolized by CYP450 enzymes (see CLINICAL PHARMACOLOGY).

Antiretroviral Agents

No drug interactions with other antiretroviral medications have been identified that would warrant alteration of either the enfuvirtide dose or the dose of the other antiretroviral medication.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Mutagenesis

Enfuvirtide was neither mutagenic nor clastogenic in a series of in vivo and in vitro assays including the Ames bacterial reverse mutation assay, a mammalian cell forward gene mutation assay in AS52 Chinese Hamster ovary cells or an in vivo mouse micronucleus assay.

Impairment of Fertility

Enfuvirtide produced no adverse effects on fertility in male or female rats at doses of up to 30 mg/kg/day administered by subcutaneous injection (1.6 times the maximum recommended adult human daily dose on a m^2 basis).

Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 27 times and 3.2 times the adult human dose on a m^2 basis. The animal studies revealed no evidence of harm to the fetus from enfuvirtide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to FUZEON and other antiretroviral drugs, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid the risk of postnatal transmission of HIV. It is not known whether enfuvirtide is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving FUZEON**.

Studies where radio-labeled ^3H-enfuvirtide was administered to lactating rats indicated that radioactivity was present in the milk. It is not known whether the radioactivity in the milk was from radio-labeled enfuvirtide or from radio-labeled metabolites of enfuvirtide (ie, amino acids and peptide fragments).

Pediatric Use

The safety and pharmacokinetics of FUZEON have not been established in pediatric subjects below 6 years of age. Limited efficacy data is available in pediatric subjects 6 years of age and older.

Thirty-five HIV-1 infected pediatric subjects ages 6 through 16 years have received FUZEON in two open-label, single-arm clinical trials. Adverse experiences were similar to those observed in adult patients.

Study T20-204 was an open-label, multicenter trial that evaluated the safety, and antiviral activity of FUZEON in treatment-experienced pediatric subjects. Eleven subjects from 6 to 12 years were enrolled (median age of 9 years). Median baseline CD4 cell count was 509 cells/µL and the median baseline HIV-1 RNA was 4.5 log_{10} copies/mL.

Ten of the 11 study subjects completed 48 weeks of chronic therapy. By week 48, 6/11 (55%) subjects had ≥1 $\log_{10}$ decline in HIV-1 RNA and 4/11 (36%) subjects were below 400 copies/mL of HIV-1 RNA. The median changes from baseline in HIV-1 RNA and CD4 cell count were -1.48 $\log_{10}$ copies/mL and 122 cells/µL, respectively.

Study T20-310 is an ongoing, open-label, multicenter trial evaluating the pharmacokinetics, safety, and antiviral activity of FUZEON in treatment-experienced pediatric subjects and adolescents. Twenty-four subjects from 6 through 16 years were enrolled (median age of 13 years). Median baseline CD4 cell count was 143 cells/µL and the median baseline HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The evaluation of the antiviral activity is ongoing.

Geriatric Use

Clinical studies of FUZEON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

The overall safety profile of FUZEON is based on 1188 subjects who received at least 1 dose of FUZEON during various clinical trials. This includes 1153 adults, 608 of whom received the recommended dose for greater than 24 weeks, and 35 pediatric subjects.

Assessment of treatment-emergent adverse events is based on the pooled data from the two Phase 3 studies T20-301 and T20-302.

Local Injection Site Reactions

Local injection site reactions were the most frequent adverse events associated with the use of FUZEON. In Phase 3 clinical studies (T20-301 and T20-302), 98% of subjects had at least 1 local injection site reaction (ISR). Three percent of subjects discontinued treatment with FUZEON because of ISRs. Eighty-six percent of subjects experienced their first ISR during the initial week of treatment. The majority of ISRs were associated with mild to moderate pain at the injection site, erythema, induration, and the presence of nodules or cysts. For most subjects the severity of signs and symptoms associated with ISRs did not change during the 24 weeks of treatment. In 17% of subjects an individual ISR lasted for longer than 7 days. Because of the frequency and duration of individual ISRs, 23% of subjects had six or more ongoing ISRs at any given time. Individual signs and symptoms characterizing local ISRs are summarized in Table 4. Infection at the injection site (including abscess and cellulitis) was reported in 1% of subjects.

Table 4. Summary of Individual Signs/Symptoms Characterizing Local Injection Site Reactions to Enfuvirtide in Studies T20-301 and T20-302 Combined (% of Subjects)

	N=663		
Event Category	**Any Severity Grade**	**% of Events Comprising Grade 3 Reactions**	**% of Events Comprising Grade 4 Reactions**
Pain/Discomfort[a]	95%	9%	0%
Induration[b]	89%	41%	16%
Erythema[c]	89%	22%	10%
Nodules and Cysts[d]	76%	26%	0%
Pruritus[e]	62%	4%	NA
Ecchymosis[f]	48%	8%	5%

[a] Grade 3 = severe pain requiring analgesics (or narcotic analgesics for ≤72 hours) and/or limiting usual activities;
Grade 4 = severe pain requiring hospitalization or prolongation of hospitalization, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.
[b] Grade 3 = ≥25 mm but <50 mm; Grade 4 = ≥50 mm average diameter.
[c] Grade 3 = ≥50 mm but <85 mm average diameter; Grade 4 = ≥85 mm average diameter.
[d] Grade 3 = ≥3 cm; Grade 4 = if draining.
[e] Grade 3 = refractory to topical treatment or requiring oral or parenteral treatment; Grade 4 = not applicable.
[f] Grade 3 = >3 cm but ≤5 cm; Grade 4 = >5 cm.

Other Adverse Events

Hypersensitivity reactions have been attributed to FUZEON (≤1%) and in some cases have recurred upon re-challenge (see WARNINGS).

The events most frequently reported in subjects receiving FUZEON+background regimen, excluding injection site reactions, were diarrhea (26.8%), nausea (20.1%), and fatigue (16.1%). These events were also commonly observed in subjects that received background regimen alone: diarrhea (33.5%), nausea (23.7%), and fatigue (17.4%).

Treatment-emergent adverse events (% of subjects), excluding ISRs, from Phase 3 studies are summarized for adult subjects, regardless of severity and causality, in Table 5. Only events occurring in ≥2% of subjects and at a higher rate in subjects treated with FUZEON are summarized in Table 5; events that occurred at a higher rate in the control arms are not displayed.

Table 5. Percentage of Patients With Selected Treatment-Emergent Adverse Events* Reported in ≥2% of Adult Patients and Occurring More Frequently in Patients Treated With FUZEON (Pooled Studies T20-301/T20-302 at 24 Weeks)

Adverse Event (by System Organ Class)	FUZEON+ Background Regimen	Background Regimen
	N=663	N=334
Nervous System Disorders		
Peripheral Neuropathy	8.9%	6.3%
Taste Disturbance	2.4%	1.5%
Psychiatric Disorders		
Insomnia	11.3%	8.7%
Depression	8.6%	7.2%
Anxiety	5.7%	3.0%
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	7.4%	5.4%
Infections		
Sinusitis	6.2%	2.1%
Herpes Simplex	5.0%	3.9%
Skin Papilloma	4.2%	1.5%
Influenza	3.9%	1.8%
General		
Weight Decreased	6.5%	5.1%
Appetite Decreased	6.3%	2.4%
Asthenia	5.7%	4.2%
Anorexia	2.6%	1.8%
Influenza-like Illness	2.3%	0.9%
Skin and Subcutaneous Tissue Disorders		
Pruritus Nos	5.1%	4.2%
Musculoskeletal, Connective Tissue, and Bone Disorders		
Myalgia	5.0%	2.4%
Gastrointestinal Disorders		
Constipation	3.9%	2.7%
Abdominal Pain Upper	3.0%	2.7%
Pancreatitis	2.4%	0.9%
Eye Disorders		
Conjunctivitis	2.4%	0.9%
Blood and Lymphatic System Disorders		
Lymphadenopathy	2.3%	0.3%

*Excludes Injection Site Reactions

An increased rate of bacterial pneumonia was observed in subjects treated with FUZEON in the Phase 3 clinical trials compared to the control arm (4.68 pneumonia events per 100 patient-years versus 0.61 events per 100 patient-years, respectively). Approximately half of the study subjects with pneumonia required hospitalization. One subject death in the FUZEON arm was attributed to pneumonia. Risk factors for pneumonia included low initial CD4 lymphocyte count, high initial viral load, intravenous drug use, smoking, and a prior history of lung disease. It is unclear if the increased incidence of pneumonia was related to FUZEON use. However, because of this finding patients with HIV infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia (see WARNINGS).

Less Common Events

The following adverse events have been reported in 1 or more subjects; however, a causal relationship to FUZEON has not been established.

Immune System Disorders: worsening abacavir hypersensitivity reaction

Renal and Urinary Disorders: renal insufficiency (glomerulonephritis); renal failure

Blood and Lymphatic Disorders: thrombocytopenia; neutropenia, and fever

Endocrine and Metabolic: hyperglycemia

Infections and Infestations: pneumonia

Nervous System Disorders: Guillain-Barre syndrome (fatal); sixth nerve palsy

Laboratory Abnormalities

Table 6 shows the treatment-emergent laboratory abnormalities that occurred in at least 2% of subjects and more frequently in those receiving FUZEON+background regimen than background regimen alone from studies T20-301 and T20-302.

Table 6. Percentage of Treatment-Emergent Laboratory Abnormalities That Occurred in ≥2% of Adult Patients and More Frequently in Patients Receiving FUZEON (Pooled Studies T20-301 and T20-302 at 24 Weeks)

Laboratory Parameters	Grading	FUZEON+ Background Regimen	Background Regimen
		N=663	N=334
Eosinophilia			
1-2 X ULN (0.7 x 10^9/L)	0.7-1.4 x 10^9/L	8.3%	1.5%
>2 X ULN (0.7 x 10^9/L)	>1.4 x 10^9/L	1.8%	0.9%
Amylase (U/L)			
Gr. 3	>2-5 x ULN	6.2%	3.6%
Gr. 4	>5 x ULN or clinical pancreatitis	0.9%	0.6%
Lipase (U/L)			
Gr. 3	>2-5 x ULN	5.9%	3.6%
Gr. 4	>5 x ULN	2.3%	1.8%
Triglycerides (mmol/L)			
Gr. 3	>1000 mg/dL	8.9%	7.2%
ALT			
Gr. 3	>5-10 x ULN	3.5%	2.1%
Gr. 4	>10 x ULN	0.9%	0.6%
AST			
Gr. 3	>5-10 x ULN	3.6%	3.0%
Gr. 4	>10 x ULN	1.2%	0.6%
Creatine Phosphokinase (U/L)			
Gr. 3	>5-10 x ULN	5.9%	3.6%
Gr. 4	>10 x ULN	2.3%	3.6%
GGT (U/L)			
Gr. 3	>5-10 x ULN	3.5%	3.3%
Gr. 4	>10 x ULN	2.4%	1.8%
Hemoglobin (g/dL)			
Gr. 3	6.5-7.9 g/dL	1.5%	0.9%
Gr. 4	<6.5 g/dL	0.6%	0.6%

Adverse Events in Pediatric Patients

FUZEON has been studied in 35 pediatric subjects 6 through 16 years of age with duration of FUZEON exposure ranging from 1 dose to 48 weeks. Adverse experiences seen during clinical trials were similar to those observed in adult subjects.

OVERDOSAGE

There are no reports of human experience of acute overdose with FUZEON. The highest dose administered to 12 subjects in a clinical trial was 180 mg as a single dose subcutaneously. There is no specific antidote for overdose with FUZEON. Treatment of overdose should consist of general supportive measures.

DOSAGE AND ADMINISTRATION

Adults

The recommended dose of FUZEON is 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site, and only where there is no current injection site reaction from an earlier dose. FUZEON should not be injected into moles, scar tissue, bruises or the navel. Additional detailed information regarding the administration of FUZEON is described in the FUZEON *Injection Instructions*.

Pediatric Patients

No data are available to establish a dose recommendation of FUZEON in pediatric patients below the age of 6 years. In pediatric patients 6 years through 16 years of age, the recommended dosage of FUZEON is 2 mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction from an earlier dose. FUZEON should not be injected into moles, scar tissue, bruises or the navel. Table 7 contains dosing guidelines for FUZEON based on body weight. Weight should be monitored periodically and the FUZEON dose adjusted accordingly.

Table 7. Pediatric Dosing Guidelines

Weight		Dose per bid Injection (mg/dose)	Injection Volume (90 mg enfuvirtide per mL)
Kilograms (kg)	**Pounds (lbs)**		
11.0 to 15.5	24 to 34	27	0.3 mL
15.6 to 20.0	>34 to 44	36	0.4 mL
20.1 to 24.5	>44 to 54	45	0.5 mL
24.6 to 29.0	>54 to 64	54	0.6 mL
29.1 to 33.5	>64 to 74	63	0.7 mL
33.6 to 38.0	>74 to 84	72	0.8 mL
38.1 to 42.5	>84 to 94	81	0.9 mL
≥42.6	>94	90	1.0 mL

Directions for Use

For more detailed instructions, see FUZEON *Injection Instructions*.

Subcutaneous Administration

FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection. After adding sterile water, the vial should be gently tapped for 10 seconds and then gently rolled between the hands to avoid foaming and to ensure all particles of drug are in contact with the liquid and no drug remains on the vial wall. The vial should then be allowed to stand until the powder goes completely into solution, which could take up to 45 minutes. Reconstitution time can be reduced by gently rolling the vial between the hands until the product is completely dissolved. Before the solution is withdrawn for administration, the vial should be inspected visually to ensure that the contents are fully dissolved in solution, and that the solution is clear, colorless and without bubbles or particulate matter. If there is evidence of particulate matter, the vial must not be used and should be returned to the pharmacy.

FUZEON contains no preservatives. Once reconstituted, FUZEON should be injected immediately or kept refrigerated in the original vial until use. Reconstituted FUZEON must be used within 24 hours. The subsequent dose of FUZEON can be reconstituted in advance and must be stored in the refrigerator in the original vial and used within 24 hours. Refrigerated reconstituted solution should be brought to room temperature before injection and the vial should be inspected visually again to ensure that the contents are fully dissolved in solution and that the solution is clear, colorless, and without bubbles or particulate matter.

The reconstituted solution should be injected subcutaneously in the upper arm, abdomen or anterior thigh. The injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction. Also, do not inject into moles, scar tissue, bruises or the navel. A vial is suitable for single use only; unused portions must be discarded (see FUZEON *Injection Instructions*).

Patients should contact their healthcare provider for any questions regarding the administration of FUZEON. Information about the self-administration of FUZEON may also be obtained by calling the toll-free number 1-877-4-FUZEON (1-877-438-9366) or at the FUZEON website, www.FUZEON.com. Patients should be taught to recognize the signs and symptoms of injection site reactions and instructed when to contact their healthcare provider about these reactions.

HOW SUPPLIED

FUZEON (enfuvirtide) for Injection is a white to off-white, sterile, lyophilized powder and it is packaged in a single-use clear glass vial containing 108 mg of enfuvirtide for the delivery of approximately 90 mg/1 mL when reconstituted with 1.1 mL of Sterile Water for Injection.

FUZEON is available in a Convenience Kit containing 60 single-use vials (2 cartons of 30 each) of FUZEON (90 mg strength), 60 vials (2 cartons of 30 each) of Sterile Water for Injection (1.1 mL per vial), 60 reconstitution syringes (3 cc), 60 administration syringes (1 cc), alcohol wipes, Package Insert, Patient Package Insert, and Injection Instruction Guide (NDC 0004-0380-39).

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Reconstituted solution should be stored under refrigeration at 2° to 8°C (36° to 46°F) and used within 24 hours.

℞ only

FUZEON has been jointly developed by Trimeris, Inc. and Hoffmann-La Roche Inc.
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